PATENT COOPERATION TREATY

7

14 MAR 2005

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

ROBERTSON, James, Alexander
Lloyd Wise, McNeight & Lawrence
Highbank House
Exchange Street
Stockport Cheshire Sk3 0ET
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 09.03.2005
Applicant's or agent's file reference MP100462-WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/001619	14.04.2004	17.04.2003

Applicant
NEUTEC PHARMA PLC et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Cleere, C Tel. +49 89 2399-7713

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference MP100462-WO	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2004/001619	International filing date *(day/month/year)* 14.04.2004	Priority date *(day/month/year)* 17.04.2003
International Patent Classification (IPC) or national classification and IPC C07K16/12, A61K39/40, C12Q1/68, G01N33/563		
Applicant NEUTEC PHARMA PLC et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.11.2004	09.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Ulbrecht, M Telephone No. +49 89 2399-7710

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/001619

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-46 as originally filed

Sequence listings part of the description, Pages

1-32 as originally filed

Claims, Numbers

1-18 received on 28.01.2005 with letter of 27.01.2005

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/001619

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-3 (partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-3 (partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/001619

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-18
	No:	Claims	
Inventive step (IS)	Yes:	Claims	4-18
	No:	Claims	1-3
Industrial applicability (IA)	Yes:	Claims	1-18
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Re Item III.

The antibodies or antigen binding fragments according to claims 1-3 are only defined by their CDR-H3 and/or CDR-L3 sequences. No other features defining the said antibodies are provided. Hence, the scope of said claims cannot be determined (Art. 6 PCT). Therefore, the search of said claims was limited to CDR-H3 and/or CDR-L3 having the sequences specified in said claims, and consequently, examination of novelty, inventive step and industrial applicability of the subject-matter of said claims will be restricted to the said searched subject-matter (Art. 66(1)(e) PCT).

Re Item V.

1. Reference is made to the following documents:

   D1: WO 00/12562 A (GENENTECH INC) 9 March 2000 (2000-03-09)
   D2: WO 97/20932 A (ALLEN DEBORAH JULIE ; CAMBRIDGE ANTIBODY TECH (GB); MCCAFFERTY JOHN GE) 12 June 1997 (1997-06-12)
   D3: DE 197 39 685 A (EICHEL STREIBER CHRISTOPH VON) 11 March 1999 (1999-03-11)
   D4: WO 03/052416 A (MATTHEWS RUTH CHRISTINE ; NEUTEC PHARMA PLC (GB); RIGG GORDON PATRICK) 26 June 2003 (2003-06-26)
   D5: HOLT L.J. ET AL., 'Domain antibodies: proteins for therapy', TRENDS IN BIOTECHNOLOGY, vol. 21, no. 11, November 2003

2. The subject-matter of claims 1-18 is novel over the prior art which does not disclose the combination of features suggested by the said claims (Art. 33(2) PCT).

3.1 Claim 1 aims at providing CDR-H3 sequences that are associated with C. difficile infection or vaccination. However, the sequences according to SEQ ID Nos. 27, 28, 30 and 31 were only detected in two C. difficile infected patients (cf. Table 12). This very limited experimental support is not considered sufficient to establish an association between the CDR-H3 sequences according to claim 1 and a C. difficile infection or vaccination (Art. 6 PCT). The finding of identical CDR sequences in two C. difficile infected patients does not automatically mean that these sequences are

indeed associated with the infection. For an association to be valid a larger sample has to be analysed and compared to an appropriate control group. Therefore, the above stated problem is not considered as being solved and consequently, the problem underlying claim 1 has to be formulated in more generic terms, namely as the provision of further CDR-H3 sequences. Provision of CDR-H3 sequences involves nothing but routine experimentation (cf. e.g. D1-D3), and hence no inventive step can be acknowledged for the subject-matter of claim 1 (Art. 33(3) PCT).

3.2 The CDR's according to SEQ ID No. 32 and 34 referred to in claim 2 are only found in a single C. difficile infected patient. Thus, the foregoing considerations (cf. V. 3.1) also apply to claim 2. Moreover, a CDR having SEQ ID No. 34 is also found in MRSA and VRE infected patients, thus being no indicator for a C. difficile infection. Consequently, no inventive step can be acknowledged for the subject-matter of claim 2 (Art. 33(3) PCT).

3.3 The same considerations as under V. 3.1 and 3.2 also apply to claim 3 which therefore is not considered inventive (Art. 33(3) PCT).

3.4 Claim 4 solves the problem of identifying candidate sequences of at least the CDR3 region of antibodies specific against at least one antigen produced by C. difficile during infection or against a vaccine. The solution involves determining in B cells CDR3 sequences that have a frequency of more than 1%. None of the prior art documents, neither alone nor taken in combination, fairly suggests the subject-matter of claim 4 which is therefore considered to involve an inventive step (Art. 33(3) PCT).

3.5 For the foregoing considerations (cf. V. 3.4) claims 17 and 18 which incorporate the said inventive methods of claim 4 are also considered inventive (Art. 33(3) PCT).

3.9 The same considerations as under V. 3.4 also apply to the dependent claims 5-16 (Art. 33(3) PCT).

4. Industrial applicability for the subject-matter of claims 1-18 is acknowledged (Art. 33(4) PCT).

5. Should the priority of the present application not be valid, the D4 would be relevant with respect to novelty and inventive step (Art. 33(2) and (3) PCT). Furthermore, should the present application be entered into the regional phase, the above document could be relevant to the question of novelty.

CLAIMS

1. An antibody or an antigen binding fragment thereof having the CDR-H3 sequence selected from the group consisting of: SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 30, and SEQ ID NO: 31.

2. An antibody or an antigen binding fragment thereof having the CDR-L3 sequence selected from the group consisting of: SEQ ID NO: 32, and SEQ ID NO: 34.

3. An antibody or an antigen binding fragment thereof having a CDR-H3 sequence selected from the group consisting of: SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 30, and SEQ ID NO: 31, and a CDR-L3 sequence selected from the group consisting of: SEQ ID NO: 32, and SEQ ID NO: 34.

4. A method for identifying candidate sequences of at least the CDR3 region of antibodies specific against at least one antigen produced by *Clostridium difficile* during an infection or against a vaccine, comprising the steps of:

   (i) with B cells isolated from at least one patient who has been infected by *Clostridium difficile* or administered said vaccine, sequencing at least the CDR3 region of the VH and/or VL coding regions of said B cells; and

   (ii) correlating said sequenced at least the CDR3 regions of the VH and/or VL coding regions of said B cells from said at least one patient to identify a set of candidate sequences for at least a CDR3 region of antibodies specific against said at least one antigen produced by *Clostridium difficile* or against said vaccine, each of said set of candidate CDR3 sequences or a sequence having at least 80%

homology therewith occurring in total at a frequency of at least 1 percent in the set of sequences determined at step (i).

5. A method according to claim 4, said B cells being selected from the group consisting of peripheral B-cell lymphocytes and B cells from the spleen.

6. A method according to claim 5, said peripheral B-cell lymphocytes being isolated from blood from said at least one patient.

7. A method according to any of claims 4-6, said at least one antigen being an immunogen.

8. A method according to any of claims 4-7, said at least one patient displaying a pronounced antibody response in response to infection by *Clostridium difficile*.

9. A method according to any of claims 4-8, said at least one patient having recovered from infection by *Clostridium difficile*.

10. A method according to any of claims 4-9, said correlation step (ii) comprising determining putative amino acid sequences from said sequenced at least the VH and/or VL CDR3 coding regions, and correlating said putative amino acid sequences.

11. A method according to claim 9, said correlation step (ii) comprising identifying the Complementarity Determining Regions comprised in said at least the VH and/or VL regions and correlating said Complementarity Determining Regions.

12. A method according to claim 11, said Complementarity Determining Regions being selected from the group consisting of CDR1, CDR2 and CDR3.

13. A method according to any of claims 4-12, said correlation step (ii) additionally correlating at least one of the group consisting of: the strain of *Clostridium difficile* infecting said at least one patient, the time point at which said B cells are isolated during infection of said at least one patient by *Clostridium difficile*, the age of said at least one patient, the sex of said at least one patient, and the race of said at least one patient.

14. A method according to any of claims 4-13, said B cells having been isolated from said at least one patient at a plurality of time points during infection of said at least one patient by *Clostridium difficile*, said correlation step (ii) correlating the time point during infection of said at least one patient by *Clostridium difficile* at which said B cells are isolated.

15. A method according to any of claims 4-13, said B cells having been isolated from at least two patients, at least one of whom has recovered from infection by *Clostridium difficile*, and at least one of whom has not recovered from infection by *Clostridium difficile*, said correlation step (ii) correlating the recovery of said at least two patients from infection by *Clostridium difficile*.

16. A method according to any of claims 4-13, said B cells having been isolated from at least two patients, said patients being infected by different strains of *Clostridium difficile* producing said at least one antigen, said correlation step (ii) correlating said sequenced at least the VH and/or VL coding regions of said B cells to identify a set of candidate sequences for antibodies, each of which is specific against at least one shared

antigen produced by said different strains of *Clostridium difficile* or is specific against different antigens produced by said different strains of *Clostridium difficile*.

17. A method of producing a database which identifies candidate sequences for antibodies specific against at least one antigen produced by *Clostridium difficile*, comprising the steps of:

(i) performing a method according to any of claims 4-16; and

(ii) storing the data produced by said method in said database.

18. A method of generating a report which identifies candidate sequences for antibodies specific against at least one antigen produced by *Clostridium difficile*, comprising the steps of:

(i) performing a method according to any of claims 4-16; and

(ii) producing a report comprising the data produced by said method.